

=> d his

(FILE 'HOME' ENTERED AT 08:38:57 ON 09 MAR 2004)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:39:07 ON 09 MAR 2004

L1 0 S HB12605 OR HB12606 OR HB12607 OR HB12608 OR HB12609 OR HB1261
L2 0 S HB() (12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610)
L3 0 S HB()12() (605 OR 606 OR 607 OR 608 OR 609 OR 610)
L4 0 S ATCC(L)12() (605 OR 606 OR 607 OR 608 OR 609 OR 610)
L5 0 S ATCC(L) (12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610)
L6 32 S 12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610
L7 0 S L6 AND (CDR OR CCR OR CCR5)
L8 0 S L6 AND ?CHEMOKIN?
L9 0 S L6 AND (MAB OR MONOCLON? OR ANTIBOD?)
L10 281 S PA8 OR PA9 OR PA10 OR PA11 OR PA12 OR PA14
L11 629 S PA() (8 OR 9 OR 10 OR 11 OR 12 OR 14)
L12 896 S L10,L11
L13 4 S L12 AND (CDR OR CCR OR CCR5)
L14 4 S L12 AND ?CHEMOKIN?
L15 4 S L13,L14
E OLSON W/AU
L16 19 S E3,E7,E8
E OLSON WILL/AU
L17 69 S E5,E10
E MADDON P/AU
L18 84 S E3-E8
E PROGENIC/PA,CS
L19 52 S E5-E16
E PROGEN/PA,CS
L20 3 S E44-E49
L21 4 S L12 AND L16-L20
L22 4 S L15,L21
L23 258 S PRO() (8 OR 80 OR 9 OR 90 OR 10 OR 100 OR 11 OR 110 OR 12 OR 1
L24 6 S L23 AND (CDR OR CCR OR CCR5)
L25 6 S L23 AND ?CHEMOKIN?
L26 6 S L24,L25
L27 5 S L26 NOT L22
SEL DN AN 1
L28 4 S L27 NOT E1-E3
L29 8 S L22,L28 AND L1-L28
E WO99-US30345/AP,PRN
L30 1 S E3,E4
SEL RN

FILE 'REGISTRY' ENTERED AT 08:51:33 ON 09 MAR 2004

L31 1 S E1

FILE 'HCAPLUS' ENTERED AT 08:51:55 ON 09 MAR 2004

L32 8 S L29,L30

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 08:52:09 ON 09 MAR 2004

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FILE COVERS 1907 - 9 Mar 2004 VOL 140 ISS 11
FILE LAST UPDATED: 8 Mar 2004 (20040308/ED)

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L32 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:246838 HCAPLUS
DN 138:236783
ED Entered STN: 31 Mar 2003
TI The CCR5 and CXCR4 coreceptors are both used by human immunodeficiency virus type 1 primary isolates from subtype C
AU Cilliers, Tonie; Nhlapo, Jabulani; Coetzer, Mia; Orlovic, Dragana; Ketas, Thomas; Olson, William C.; Moore, John P.; Trkola, Alexandra; Morris, Lynn
CS AIDS Virus Research Unit, National Institute for Communicable Diseases, Johannesburg, 2131, S. Afr.
SO Journal of Virology (2003), 77(7), 4449-4456
CODEN: JOVIAM; ISSN: 0022-538X
PB American Society for Microbiology
DT Journal
LA English
CC 15-8 (Immunochemistry)
AB Human immunodeficiency virus type 1 (HIV-1) subtype C viruses with different coreceptor usage profiles were isolated from 29 South African patients with advanced AIDS. All 24 R5 isolates were inhibited by the CCR5-specific agents, PRO 140 and RANTES, while the two X4 viruses and the three R5X4 viruses were sensitive to the CXCR4-specific inhibitor, AMD3100. The five X4 or R5X4 viruses were all able to replicate in peripheral blood mononuclear cells that did not express CCR5. When tested using coreceptor-transfected cell lines, one R5 virus was also able to use CXCR6, and another R5X4 virus could use CCR3, BOB/GPR15, and CXCR6. The R5X4 and X4 viruses contained more-diverse V3 loop sequences, with a higher overall pos. charge, than the R5 viruses. Hence, some HIV-1 subtype C viruses are able to use CCR5, CXCR4, or both CXCR4 and CCR5 for entry, and they are sensitive to specific inhibitors of entry via these coreceptors. These observations are relevant to understanding the rapid spread of HIV-1 subtype C in the developing world and to the design of intervention and treatment strategies.
ST HIV1 subtype C CCR5 CXCR4 coreceptor T lymphocyte
IT Chemokine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (CCR5; HIV-1 subtype C can use both CCR5 and CXCR4 coreceptors)
IT Chemokine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (CXCR4; HIV-1 subtype C can use both CCR5 and CXCR4 coreceptors)
IT AIDS (disease)
Human
Human immunodeficiency virus 1
Protein sequences
(HIV-1 subtype C can use both CCR5 and CXCR4 coreceptors)
IT Envelope proteins

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(HIV-1 subtype C can use both CCR5 and CXCR4 coreceptors)

IT CD4-positive T cell

(disease, infection; HIV-1 subtype C can use both CCR5 and CXCR4 coreceptors)

IT DNA sequences

Viral RNA sequences

(for envelope protein V3 loop fragments of human immunodeficiency virus)

IT 502130-81-6

RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)

(nucleotide sequence; HIV-1 subtype C can use both CCR5 and CXCR4 coreceptors)

IT 502130-83-8 502130-85-0 502130-87-2 502130-89-4 502130-91-8

502130-93-0 502130-95-2 502130-97-4 502130-99-6 502131-01-3

502131-05-7 502131-07-9 502131-09-1

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(nucleotide sequence; HIV-1 subtype C can use both CCR5 and CXCR4 coreceptors)

RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L32 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:174230 HCAPLUS

DN 138:215262

ED Entered STN: 07 Mar 2003

TI Methods for inhibiting HIV-1 infection with antibody binding to
CCR5 chemokine receptor or inhibiting HIV-1 fusion with
 cell positive for CD4 and **CCR5**

IN Olson, William C.; Maddon, Paul J.

PA USA

SO U.S. Pat. Appl. Publ., 50 pp.

CODEN: USXXCO

DT Patent

LA English

IC ICM A61K039-395

ICS A61K039-42

NCL 424144100; 424160100

CC 1-5 (Pharmacology)

Section cross-reference(s): 15

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003044411	A1	20030306	US 2002-116797	20020405
PRAI	US 2001-282380P	P	20010406		

AB This invention provides a method of reducing an HIV infected subject's
 HIV-1 viral load which comprises administering to the subject an effective
 viral load reducing amount of an antibody which (a) binds to a **CCR5**
chemokine receptor and (b) inhibits fusion of HIV-1 to a CD4+
CCR5+cell, so as to thereby reduce the subject's HIV-1 viral load
 to 50% or less of the subject's HIV-1 viral load prior to administering
 the antibody to the subject. A single 1 mg dose of anti-**CCR5**
 monoclonal antibody **PA14** gave potent antiviral activity in the
 hu-PBL-SCID mouse model of HIV-1 infection.

ST HIV1 infection inhibition antibody **CCR5 chemokine**
 receptor

- IT **Chemokine receptors**
 RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
 (CCR5; inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)
- IT **Immunoglobulins**
 RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (G1, monoclonal; inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)
- IT **Immunoglobulins**
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (G2, fusion proteins with CD4, binding to gp120, synergistic inhibition of HIV-1 fusion using anti-CCR5 and; inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)
- IT **CD4 (antigen)**
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (cell pos. for CCR5 and for; inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)
- IT **Hybridoma**
 (for monoclonal antibody production; inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)
- IT **Envelope proteins**
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (gp120env, CD4-IgG2 binding to, synergistic inhibition of HIV-1 fusion using anti-CCR5 and; inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)
- IT **Antibodies**
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (humanized; inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)
- IT **AIDS (disease)**
 Anti-AIDS agents
 Fusion, biological
 Human
 Human immunodeficiency virus 1
 Infection
 (inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)
- IT **Antibodies**
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)
- IT **Drug delivery systems**
 (injections, i.m.; inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)
- IT **Drug delivery systems**

- (injections, i.p.; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT Drug delivery systems
(injections, i.v.; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT Drug delivery systems
(injections, s.c.; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT Antibodies
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT Drug delivery systems
(oral; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT RANTES (**chemokine**)
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic inhibition of HIV-1 fusion using anti-**CCR5** monoclonal antibody and; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT Drug interactions
(synergistic; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT Drug delivery systems
(topical; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT Fusion proteins (chimeric proteins)
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(with CD4 and anti-gp120 IgG2; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT 500750-90-3
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequences; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT 159519-65-0, T 20 Peptide
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(and CD4-IgG2 and anti-**CCR5** synergistic inhibition of env-mediated membrane fusion; inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and **CCR5**)
- IT 500753-56-0 500753-57-1
RL: PRP (Properties)
(unclaimed protein sequence; methods for inhibiting HIV-1 infection with antibody binding to **CCR5 chemokine** receptor or

inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)

IT 352430-58-1
 RL: PRP (Properties)
 (unclaimed sequence; methods for inhibiting HIV-1 infection with antibody binding to CCR5 chemokine receptor or inhibiting HIV-1 fusion with cell pos. for CD4 and CCR5)

L32 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 2003:98579 HCAPLUS
 DN 138:186210
 ED Entered STN: 09 Feb 2003
 TI Human immunodeficiency virus type 1 attachment, coreceptor, and fusion inhibitors are active against both direct and trans infection of primary cells
 AU Ketas, Thomas J.; Frank, Ines; Klasse, Per Johan; Sullivan, Brian M.; Gardner, Jason P.; Spenlehauer, Catherine; Nesin, Mirjana; Olson, William C.; Moore, John P.; Pope, Melissa
 CS Progenics Pharmaceuticals, Inc., Tarrytown, NY, 10591, USA
 SO Journal of Virology (2003), 77(4), 2762-2767
 CODEN: JOVIAM; ISSN: 0022-538X
 PB American Society for Microbiology
 DT Journal
 LA English
 CC 15-8 (Immunochemistry)
 AB Inhibitors of human immunodeficiency virus type 1 attachment (CD4-IgG subclass 2), CCR5 usage (PRO 140), and fusion (T-20) were tested on diverse primary cell types that represent the major targets both for infection in vivo and for the inhibition of trans infection of target cells by virus bound to dendritic cells. Although minor cell-type-dependent differences in potency were observed, each inhibitor was active on each cell type and trans infection was similarly vulnerable to inhibition at each stage of the fusion cascade.
 ST HIV1 adhesion leukocyte CD4 antigen CCR5 receptor
 IT Chemokine receptors
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (CCR5; human immunodeficiency virus type 1 attachment, coreceptor, and fusion inhibitors are active against both direct and trans infection of primary cells)
 IT Immunoglobulins
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (G2; human immunodeficiency virus type 1 attachment, coreceptor, and fusion inhibitors are active against both direct and trans infection of primary cells)
 IT Adhesion, biological
 Dendritic cell
 Fusion, biological
 Human
 Human immunodeficiency virus 1
 Macrophage
 Mononuclear cell (leukocyte)
 (human immunodeficiency virus type 1 attachment, coreceptor, and fusion inhibitors are active against both direct and trans infection of primary cells)
 IT CD4 (antigen)
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (human immunodeficiency virus type 1 attachment, coreceptor, and fusion inhibitors are active against both direct and trans infection of primary cells)

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L32 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:153944 HCAPLUS

DN 136:293396

ED Entered STN: 28 Feb 2002

TI Identification of amino acid residues critical for LD78 β , a variant of human macrophage inflammatory protein-1 α , binding to CCR5 and inhibition of R5 human immunodeficiency virus type 1 replication

AU Miyakawa, Toshikazu; Obaru, Kenshi; Maeda, Kenji; Harada, Shigeyoshi; Mitsuya, Hiroaki

CS Department of Internal Medicine II, Kumamoto University School of Medicine, Kumamoto, 860-0811, Japan

SO Journal of Biological Chemistry (2002); 277(7); 4649-4655

CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

CC 15-8 (Immunochemistry)

AB In an attempt to determine which amino acid(s) of LD78 β , a variant of human macrophage inflammatory protein-1 α , plays a critical role in the interaction with CCR5, we generated six LD78 β variants with an amino acid substituted to Ala at the NH2 terminus of LD78 β . There was no significant difference in eliciting Ca²⁺ flux and chemotaxis among the variants with the exception of LD78 β T9A showing a substantially reduced activity. The comparative order for human immunodeficiency virus

type 1 (HIV-1) replication inhibition was: LD78βP8A > LD78βD6A > LD78βWT, LD78βL3A > LD78βT7A, LD78βP2A > LD78βT9A. In binding inhibition assays of LD78β variants using 2D7 monoclonal antibody and 125I-labeled macrophage inflammatory protein-1α, the comparative order was: LD78βP8A, LD78βD6A > LD78βWT > LD78βL3A > LD78βT7A > LD78βT9A, LD78βP2A. The order for CCR5 down-regulation induction was comparable to that for binding inhibition. The present data suggest that Pro-2, Asp-6, Pro-8, and Thr-9 are critical for LD78β binding to CCR5 and HIV-1 replication inhibition, and that LD78β binding to CCR5, regardless of affinity, is sufficient for the initial signal transduction of LD78β, whereas the greater anti-HIV-1 activity requires the greater magnitude of binding. The data also suggest that LD78β variants with appropriate amino acid substitution(s) such as LD78βD6A and LD78βP8A may represent effective chemokine-based anti-HIV-1 therapeutics while preserving LD78β-CCR5 interactions.

ST HIV replication inhibition macrophage inflammatory protein CCR5

IT Chemokine receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study) (CCR5; identification of amino acid residues critical for LD78β, a variant of human macrophage inflammatory protein-1α, binding to CCR5 and inhibition of R5 HIV-1 virus replication)

IT Human

Protein sequences

Signal transduction, biological

(identification of amino acid residues critical for LD78β, a variant of human macrophage inflammatory protein-1α, binding to CCR5 and inhibition of R5 HIV-1 virus replication)

IT Transcriptional regulation

(repression; identification of amino acid residues critical for LD78β, a variant of human macrophage inflammatory protein-1α, binding to CCR5 and inhibition of R5 HIV-1 virus replication)

IT Macrophage inflammatory protein 1α

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(variants; identification of amino acid residues critical for LD78β, a variant of human macrophage inflammatory protein-1α, binding to CCR5 and inhibition of R5 HIV-1 virus replication)

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L32 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:905720 HCAPLUS

DN 137:72329

ED Entered STN: 16 Dec 2001

TI **PRO-140**(Progenics)

AU Poli, Guido

CS Istituto Scientifico H San Raffaele, Milan, 20132, Italy

SO IDrugs (2001), 4(9), 1068-1071

CODEN: IDRUFN; ISSN: 1369-7056

PB Current Drugs Ltd.

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

Section cross-reference(s): 15

AB A review. **PRO-140**, a monoclonal antibody against the HIV coreceptor **CCR5**, is under investigation by Progenics and the Aaron Diamond AIDS Research Center (ADARC) as a potential treatment for HIV infection [211441], [286246], [286247]. Phase I/II trials were expected to commence during 2001 [395621], [409142], despite being initially planned for 2000 [322637], [361819], [365216], [375598], [408483]. In Jan. 1998, ADARC and Progenics reported that the HIV binding site on the **CCR5** coreceptor is distinct from beta-**chemokine** binding domains, which they claimed may allow for the development of therapeutics with fewer side effects [273391], [421256]. In vitro studies have shown **PRO-140** potentially blocked all of 17 primary-HIV isolates that use **CCR5** as a fusion coreceptor [342173]. In Oct. 2000, Progenics was awarded an SBIR grant to fund a 2-yr project exploring the breadth, potency and durability of **PRO-140** therapy in laboratory and animal models of HIV infection. This project was a collaboration between Progenics, Weill Medical College of Cornell University and the Scripps Research Institute [385982]. In May 1999, the company entered into an agreement with Protein Design Labs (PDL) for the humanization by PDL of **PRO-140** [325445]. In Nov. 1997, Progenics was awarded a \$600,000 grant from the NIAID for the examination of new approaches to HIV vaccine design based on **CCR5** [268407].

ST review mAb **PRO 140** potential HIV antiviral drug

IT **Chemokine** receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(CCR5; IgG1 mAb PRO-140: potential HIV antiviral drug)

IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(G1, monoclonal, PRO-140; IgG1 mAb PRO-140: potential HIV antiviral drug)

IT Antiviral agents
Human immunodeficiency virus 1
(IgG1 mAb PRO-140: potential HIV antiviral drug)

IT Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonist; IgG1 mAb PRO-140: potential HIV antiviral drug)

IT 339183-09-4, CCR5 antibody
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IgG1 mAb PRO-140: potential HIV antiviral drug)

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L32 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:15173 HCAPLUS

DN 134:192003

ED Entered STN: 08 Jan 2001

TI Potent, broad-spectrum inhibition of human immunodeficiency virus type 1 by the CCR5 monoclonal antibody PRO 140

AU Trkola, Alexandra; Ketas, Thomas J.; Nagashima, Kirsten A.; Zhao, Lu; Cilliers, Tonie; Morris, Lynn; Moore, John P.; Maddon, Paul J.; Olson, William C.

CS The Aaron Diamond AIDS Research Center, NY, USA

SO Journal of Virology (2001), 75(2), 579-588
CODEN: JOVIAM; ISSN: 0022-538X

PB American Society for Microbiology

DT Journal

LA English

CC 15-3 (Immunochemistry)

AB CCR5 serves as a requisite fusion coreceptor for clin. relevant strains of human immunodeficiency virus type 1 (HIV-1) and provides a promising target for antiviral therapy. However, no study to date has examined whether monoclonal antibodies, small mols., or other non-chemokine agents possess broad-spectrum activity against the major genetic subtypes of HIV-1. PRO 140 (PA14) is an anti-CCR5 monoclonal antibody that potently inhibits HIV-1 entry at concns. that do not affect CCR5's chemokine receptor activity. In this study, PRO 140 was tested against a panel of primary HIV-1 isolates selected for their genotypic and geog. diversity. In quant. assays of viral infectivity, PRO 140 was compared with RANTES, a natural CCR5 ligand that can inhibit HIV-1 entry by receptor down-regulation as well as receptor blockade. Despite their divergent mechanisms of action and binding epitopes on CCR5, low nanomolar concns. of both PRO

140 and **RANTES** inhibited infection of primary peripheral blood mononuclear cells (PBMC) by all **CCR5**-using (R5) viruses tested. This is consistent with there being a highly restricted pattern of **CCR5** usage by R5 viruses. In addition, a panel of 25 subtype C South African R5 viruses were broadly inhibited by **PRO 140**, **RANTES**, and **TAK-779**, although .apprx.30-fold-higher concns. of the last compound were required. Interestingly, significant inhibition of a dual-tropic subtype C virus was also observed Whereas **PRO 140** potentially inhibited HIV-1 replication in both PBMC and primary macrophages, **RANTES** exhibited limited antiviral activity in macrophage cultures. Thus **CCR5**-targeting agents such as **PRO 140** can demonstrate potent and genetic-subtype-independent anti-HIV-1 activity.

- ST immunodeficiency virus infection **CCR5** receptor monoclonal antibody
- IT Immunoglobulins
 - RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 - (G1, monoclonal, **PRO 140**; monoclonal antibody to **CCR-5** receptor inhibits infection and replication by heterologous human immunodeficiency virus strains)
- IT Macrophage
 - (infection; monoclonal antibody to **CCR-5** receptor inhibits infection and replication by heterologous human immunodeficiency virus strains)
- IT Human immunodeficiency virus 1
 - Mononuclear cell (leukocyte)
 - (monoclonal antibody to **CCR-5** receptor inhibits infection and replication by heterologous human immunodeficiency virus strains)
- IT Anti-AIDS agents
 - (monoclonal antibody to **CCR-5** receptor inhibits infection and replication by heterologous human immunodeficiency virus strains in relation to)
- IT Infection
 - (viral; monoclonal antibody to **CCR-5** receptor inhibits infection and replication by heterologous human immunodeficiency virus strains)
- IT **Chemokine** receptors
 - RL: BSU (Biological study, unclassified); BIOL (Biological study)
 - (β **chemokine** receptor **CCR5**; monoclonal antibody to **CCR-5** receptor inhibits infection and replication by heterologous human immunodeficiency virus strains)

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L32 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:420924 HCAPLUS
DN 133:57579

ED Entered STN: 23 Jun 2000
 TI Synergistic inhibition of HIV-1 attachment and cell fusion
 IN Olson, William C.; Maddon, Paul J.
 PA Progenics Pharmaceuticals, Inc., USA
 SO PCT Int. Appl., 68 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K
 CC 15-3 (Immunochemistry)
 Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000035409	A2	20000622	WO 1999-US30345	19991216 <--
	WO 2000035409	A3	20000914		
	W: AU, CA, JP, MX				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2355607	AA	20000622	CA 1999-2355607	19991216 <--
	AU 2000021996	A1	20000703	AU 2000-21996	19991216 <--
	EP 1144006	A2	20011017	EP 1999-966466	19991216 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT , LT , LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	US 1998-112532P	P	19981216		
	US 1998-212793	A	19981216		
	WO 1999-US30345	W	19991216	<--	

AB The authors disclose the inhibition of envelope-mediated fusion and human immunodeficiency virus-1 infection by the application of at least two compds. which act synergistically. In one example, pairs of monoclonal antibodies directed against the HIV-1 co-receptor **CCR5** were synergistic in their inhibition of cellular binding by gp120/sCD4. In a second example, anti-**CCR5** monoclonal antibody **PA12** was synergistic with RANTES in blocking cell-cell fusion.

ST HIV cell fusion antibody **CCR5 chemokine** receptor;

IT immunodeficiency virus attachment **CCR5** receptor antibody

IT Immunoglobulins

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(G1, monoclonal; to **chemokine** receptors for synergistic inhibition of human immunodeficiency virus attachment and cell fusion)

IT Immunoglobulins

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(G2, fusion products, with CD4; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus by interference with envelope protein binding by)

IT Gene, animal

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(IGL; for antibody chain mediating synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT Gene, animal

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(Igh; for antibody chain mediating synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT **Chemokines**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(SDF-1 (stromal-derived factor-1); for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

- IT RANTES (**chemokine**)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs.; for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)
- IT Epitopes
(for anti-CCR5 antibodies mediating synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)
- IT RNA
cDNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(for antibody chain mediating synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)
- IT Macrophage inflammatory protein 1 α
Macrophage inflammatory protein 1 β
RANTES (**chemokine**)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)
- IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments; for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)
- IT **Chemokine** receptors
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(fusin; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus with monoclonal antibodies to)
- IT CD4 (antigen)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fusion products, with IgG2; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus by interference with envelope protein binding by)
- IT Envelope proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gp120env; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus by interference with binding to)
- IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heavy chains; for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)
- IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized; for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)
- IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(light chains; for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)
- IT Anti-AIDS agents
(monoclonal antibodies to **chemokine** receptors for synergistic inhibition of human immunodeficiency virus attachment and cell fusion)
- IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; to **chemokine** receptors for synergistic inhibition of human immunodeficiency virus attachment and cell fusion)

IT Human immunodeficiency virus 1
(synergistic inhibition of attachment and cell fusion by)

IT Cell adhesion
Cell fusion
(synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT CD4 (antigen)
Envelope proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(synergistic inhibition of attachment and cell fusion by human immunodeficiency virus by interference with binding to)

IT Infection
(viral; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

IT **Chemokine** receptors
Chemokine receptors
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(β **chemokine** receptor **CCR5**; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus with monoclonal antibodies to)

IT **Chemokines**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β , receptor **CCR5**; synergistic inhibition of attachment and cell fusion by human immunodeficiency virus with monoclonal antibodies to)

IT 155148-31-5, AMD3100
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for synergistic inhibition of attachment and cell fusion by human immunodeficiency virus)

L32 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN ✓

AN 1999:263464 HCAPLUS

DN 131:57557

ED Entered STN: 30 Apr 1999

TI Differential inhibition of human immunodeficiency virus type 1 fusion, gp120 binding, and CC-**chemokine** activity by monoclonal antibodies to **CCR5**

AU **Olson, William C.**; Rabut, Gwenael E. E.; Nagashima, Kirsten A.; Tran, Diep N. H.; Anselma, Deborah J.; Monard, Simon P.; Segal, Jeremy P.; Thompson, Daniah A. D.; Kajumo, Francis; Guo, Yong; Moore, John P.; **Maddon, Paul J.**; Dragic, Tatjana

CS Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY, 10016, USA

SO Journal of Virology (1999), 73(5), 4145-4155
CODEN: JOVIAM; ISSN: 0022-538X

PB American Society for Microbiology

DT Journal

LA English

CC 15-3 (Immunochemistry)

AB The CC-**chemokine** receptor **CCR5** mediates fusion and entry of the most commonly transmitted human immunodeficiency virus type 1 (HIV-1) strains. The authors have isolated 6 new anti-**CCR5** murine monoclonal antibodies (MAbs), designated **PA8**, **PA9**, **PA10**, **PA11**, **PA12**, and **PA14**. A panel of **CCR5** alanine point mutants was used to map the epitopes of these MAbs and the previously described MAb 2D7 to specific amino acid residues in the N terminus and/or second extracellular loop regions of **CCR5**. This structural information was correlated with the MAbs' abilities to inhibit (1) HIV-1 entry, (2) HIV-1 envelope glycoprotein-mediated membrane fusion, (3) gp120 binding to **CCR5**, and (4) CC-**chemokine** activity. Surprisingly, there was no correlation between the ability of a MAb to inhibit HIV-1 fusion-entry and

its ability to inhibit either the binding of a gp120-soluble CD4 complex to CCR5 or CC-chemokine activity. MABs PA9-PA12, whose epitopes include residues in the CCR5 N terminus, strongly inhibited gp120 binding but only moderately inhibited HIV-1 fusion and entry and had no effect on RANTES-induced calcium mobilization. MABs PA14 and 2D7, the most potent inhibitors of HIV-1 entry and fusion, were less effective at inhibiting gp120 binding and were variably potent at inhibiting RANTES-induced signaling. With respect to inhibiting HIV-1 entry and fusion, PA12 but not PA14 was potentially synergistic when used in combination with 2D7, RANTES, and CD4-IgG2, which inhibits HIV-1 attachment. The data support a model wherein HIV-1 entry occurs in 3 stages: receptor (CD4) binding, coreceptor (CCR5) binding, and coreceptor-mediated membrane fusion. These antibodies will be useful for further dissecting these events.

- ST HIV gp120 monoclonal antibody CCR5 chemokine receptor
- IT Chemokines
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (C-C; epitope mapping of monoclonal antibodies to chemokine receptor CCR5)
- IT Immunoglobulins
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (G1, monoclonal; differential inhibition of HIV-1 fusion, gp120 binding, and CC-chemokine activity by monoclonal antibodies to CCR5 receptor)
- IT Fusion, biological
 Human immunodeficiency virus 1
 (differential inhibition of HIV-1 fusion, gp120 binding, and CC-chemokine activity by monoclonal antibodies to CCR5 receptor)
- IT Envelope proteins
 RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
 (gp120env; differential inhibition of HIV-1 fusion, gp120 binding, and CC-chemokine activity by monoclonal antibodies to CCR5 receptor)
- IT Epitopes
 (mapping; epitope mapping of monoclonal antibodies to chemokine receptor CCR5)
- IT Chemokine receptors
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (β chemokine receptor CCR5; differential inhibition of HIV-1 fusion, gp120 binding, and CC-chemokine activity by monoclonal antibodies to CCR5 receptor)
- IT 200803-28-7 200803-29-8 228120-60-3 228120-61-4
 RL: PRP (Properties)
 (epitope mapping of monoclonal antibodies to chemokine receptor CCR5)

RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L44 ANSWER 9 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2004:48240 BIOSIS
 DN PREV200400050360
 TI Immunotoxicology of **PRO 140**: A humanized anti-CCR5 monoclonal antibody for HIV-1 therapy.
 AU Gardner, J. [Reprint Author]; Cohen, M. [Reprint Author]; Rosenfield, S. I. [Reprint Author]; Nagashima, K. A. [Reprint Author]; **Maddon, P. J.** [Reprint Author]; **Olson, W. C.** [Reprint Author]
 CS **Progenics Pharmaceuticals Inc., Tarrytown, NY, USA**
 SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2003) Vol. 43, pp. 320. print.
 Meeting Info.: 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, USA. September 14-17, 2003. American Society for Microbiology.
 DT Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LA English
 ED Entered STN: 21 Jan 2004
 Last Updated on STN: 21 Jan 2004
 AB Background: The chemokine receptor CCR5 is a requisite fusion coreceptor for primary HIV-1 isolates and provides a promising target for a new generation of antiretroviral agents. **PRO 140** is a humanized anti-CCR5 monoclonal antibody (mAb) that broadly and potently blocks CCR5-mediated HIV-1 entry without CCR5 antagonism, thus offering a distinct therapeutic profile compared to small-molecule CCR5 antagonists in development. Immunotoxicology is an emerging field that examines the potential impact of drugs on immune system function. Here we report the findings of immunotoxicology studies performed using **PRO 140** prior to initiation of Phase 1 clinical testing. Methods: **PRO 140** was tested in a battery of in vitro assays of immune system function mediated by chemokine and non-chemokine mechanisms, and the immunologic activity of **PRO 140** was compared with its antiviral activity. Results: At concentrations that provide complete control of HIV-1 replication (apprx4 mug/mL), **PRO 140** had no effect on CCR5 signaling in response to CC-chemokines. Similarly, at concentrations ranging to 100 mug/mL, **PRO 140** had no effect on lymphocyte proliferation in response to mitogenic and allogeneic stimulation. Consistent with its IgG4,kappa subtype, **PRO 140** did not demonstrate significant binding to cells that express high levels of FcgammaR1 (CD64) and other Fc receptors. Lastly, **PRO 140** did not mediate significant levels of antibody-dependent cellular cytotoxicity or complement-dependent lysis of CCR5-expressing target cells. Conclusions: **PRO 140** did not interfere with normal immune system function in vitro, consistent with its lack of CCR5 antagonism and Fc-mediated effector activity. As an immunologically silent inhibitor of CCR5-mediated HIV-1 entry, **PRO 140** may offer distinct tolerability and therapeutic profiles in man.
 CC General biology - Symposia, transactions and proceedings 00520
 Cytology - General 02502
 Cytology - Animal 02506
 Cytology - Human 02508
 Biochemistry studies - General 10060
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Pathology - Therapy 12512
 Blood - Blood and lymph studies 15002
 Blood - Blood cell studies 15004
 Endocrine - General 17002
 Pharmacology - General 22002
 Pharmacology - Clinical pharmacology 22005
 Toxicology - General and methods 22501

Virology - General and methods 33502
 Immunology - General and methods 34502
 Immunology - Immunopathology, tissue immunology 34508
 Medical and clinical microbiology - Virology 36006
 Chemotherapy - General, methods and metabolism 38502
 Chemotherapy - Antiviral agents 38506

IT Major Concepts
 Biochemistry and Molecular Biophysics; Cell Biology; Immune System
 (Chemical Coordination and Homeostasis); Infection; Pharmacology;
 Toxicology

IT Parts, Structures, & Systems of Organisms
 cells; immune system: immune system, functions; lymphocytes: blood and
 lymphatics, immune system

IT Diseases
 HIV-1 infection: immune system disease, viral disease, drug therapy,
 human immunodeficiency virus 1 infection
 HIV Infections (MeSH)

IT Diseases
 viral infection: viral disease, drug therapy
 Virus Diseases (MeSH)

IT Chemicals & Biochemicals
 CCR5 chemokine receptor: antagonists, functions; IgG [immunoglobulin
 G]; **PRO 140**: antiinfective-drug, antiviral-drug,
 applications, clinical uses/effects, humanized anti-CCR5 monoclonal
 antibody; antibodies; chemokines; complement; proteins

IT Methods & Equipment
 antiviral therapy: clinical techniques, therapeutic and prophylactic
 techniques

IT Miscellaneous Descriptors
 drug development; immunotoxicology; therapeutics; viral entry:
 inhibition; viral replication: control

ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 human (common)
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
 Retroviridae 03305
 Super Taxa
 DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
 Organism Name
 HIV-1 (miscellaneous) [Human immunodeficiency virus 1 (species)]:
 pathogen
 Taxa Notes
 DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

ORGN Classifier
 Viruses 03000
 Super Taxa
 Microorganisms
 Organism Name
 Virus (common): pathogen, inhibition studies
 Taxa Notes
 Microorganisms, Viruses

L44 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2003:287881 BIOSIS
 DN PREV200300287881
 TI The humanized anti-CCR5 antibody **PRO 140** effectively
 inhibits HIV-1 entry without inhibiting RANTES-induced calcium
 mobilization.

AU O'Hara, B. [Reprint Author]; Gardner, J. P. [Reprint Author]; Ketas, T. J. [Reprint Author]; Sullivan, B. M. [Reprint Author]; Rosenfield, S. I. [Reprint Author]; Nagashima, K. A. [Reprint Author]; Maddon, P. J. [Reprint Author]; Olson, W. C. [Reprint Author]

CS **Progenics Pharmaceuticals, Inc., Tarrytown, NY, USA**

SO Antiviral Research, (February 2003) Vol. 57, No. 3, pp. A53. print.
Meeting Info.: Sixteenth International Conference on Antiviral Research.
Savannah, GA, USA. April 27-May 01, 2003.
ISSN: 0166-3542 (ISSN print).

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 19 Jun 2003
Last Updated on STN: 1 Aug 2003

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Minerals 10069
Biophysics - Membrane phenomena 10508
Pathology - Therapy 12512
Pharmacology - General 22002
Virology - General and methods 33502
Immunology - General and methods 34502
Medical and clinical microbiology - Virology 36006
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antiviral agents 38506

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection;
Pharmacology

IT Parts, Structures, & Systems of Organisms
dendritic cells: immune system

IT Chemicals & Biochemicals
CCR5; PR 140: antiinfective-drug, antiviral-drug; RANTES; calcium:
mobilization

IT Miscellaneous Descriptors
HIV entry

ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
HIV-1 (miscellaneous) [Human immunodeficiency virus 1 (species)]:
pathogen
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

RN 14191-75-4 (PR 140)
7440-70-2 (calcium)

L44 ANSWER 11 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 2003:347815 BIOSIS

DN PREV200300347815

TI Inhibition of HIV-1 entry without receptor antagonism by the humanized
anti-CCR5 antibody **PRO 140**.

AU Olson, W. C. [Reprint Author]; Gardner, J. P. [Reprint Author];
Ketas, T. J. [Reprint Author]; Sullivan, B. M. [Reprint Author];
Rosenfield, S. I. [Reprint Author]; Nagashima, K. A. [Reprint Author];
Moore, J. P.; Maddon, P. J. [Reprint Author]

CS **Progenics Pharmaceuticals, Inc., Tarrytown, NY, USA**

SO Abstracts of the Interscience Conference on Antimicrobial Agents and
Chemotherapy, (2002) Vol. 42, pp. 264. print.
Meeting Info.: 42nd Interscience Conference on Antimicrobial Agents and
Chemotherapy. San Diego, CA, USA. September 27-30, 2002. American Society
for Microbiology.

DT Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 30 Jul 2003
 Last Updated on STN: 30 Jul 2003

AB Background: CCR5 is a requisite fusion coreceptor for primary HIV-1 isolates and provides a promising target for a new generation of antiretroviral agents. **PRO 140** is an anti-CCR5 monoclonal antibody (mAb) that broadly and potently blocks R5 virus entry (Trkola et al., J. Virol. 75:579, 2001). The parent mouse antibody was recently humanized to support repeat dosing in man, and humanized **PRO 140** is entering Phase 1 clinical testing. Methods: Humanized **PRO 140** was comparatively evaluated for its breadth of antiviral activity and effects on human immune cells in vitro. The antiviral activity was examined using both whole-virus p24 assays and a novel fluorometric membrane fusion assay. The virologic studies examined a broad range of wild-type and drug-resistant HIV-1 isolates and diverse primary target cell types. Immunologic studies explored the mAb's effects on both chemokine and non-chemokine signaling pathways. Results: **PRO 140** was broadly active in blocking HIV-1 replication in diverse and clinically relevant primary target cells, such as T cells, macrophages, and dendritic cells (DCs). The median IC90 values for the different viruses and cell types clustered about 5 mug/mL. This agent was similarly effective in blocking infection of T cells by DC-associated virus in trans. Complete suppression of viral replication was obtained at **PRO 140** concentrations that had little or no effect on CC-chemokine signaling through CCR5 and other normal immunologic activities. Conclusions: Humanized **PRO 140** broadly and potently blocks HIV-1 entry through CCR5 without interfering with the receptor's normal activity. This unique and compelling therapeutic profile warrants advancement of humanized **PRO 140** into human clinical testing.

CC General biology - Symposia, transactions and proceedings 00520
 Cytology - General 02502
 Cytology - Animal 02506
 Cytology - Human 02508
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Biophysics - Membrane phenomena 10508
 Pathology - General 12502
 Pathology - Therapy 12512
 Blood - Blood and lymph studies 15002
 Blood - Blood cell studies 15004
 Pharmacology - General 22002
 Pharmacology - Clinical pharmacology 22005
 Virology - General and methods 33502
 Immunology - General and methods 34502
 Medical and clinical microbiology - Virology 36006
 Chemotherapy - Antiviral agents 38506

IT Major Concepts
 Cell Biology; Human Medicine (Medical Sciences); Immune System
 (Chemical Coordination and Homeostasis); Infection; Pharmacology

IT Parts, Structures, & Systems of Organisms
 T-cells: blood and lymphatics, immune system; dendritic cells: immune system; macrophage: blood and lymphatics, immune system

IT Diseases
 viral infection: viral disease, drug therapy
 Virus Diseases (MeSH)

IT Chemicals & Biochemicals
 CCR5: requisite fusion coreceptor; **PRO 140**
 humanized anti-CCR5 antibody: biological effects, pharmacological effects; antibodies; monoclonal antibodies: uses; proteins

IT Methods & Equipment
 antiviral therapy: clinical techniques, therapeutic and prophylactic

techniques; drug therapy: clinical techniques, therapeutic and prophylactic techniques

IT Miscellaneous Descriptors
new drug discovery; receptor antagonism; viral replication: suppression; virologic studies: results

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
HIV-1 (miscellaneous) [Human immunodeficiency virus 1 (species)]: pathogen, host cell entry inhibition
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

ORGN Classifier
Viruses 03000
Super Taxa
Microorganisms
Organism Name
virus (common): pathogen
Taxa Notes
Microorganisms, Viruses

L44 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:565842 BIOSIS
DN PREV200200565842
TI The HIV-1 entry inhibitor **PRO 140** potently and durably suppresses viral replication in vitro and in vivo.
AU **Olson, W. C.** [Reprint author]; **Franti, M.**; **Ketas, T. J.** [Reprint author]; **Nagashima, K. A.** [Reprint author]; **Maddon, P. J.** [Reprint author]; **Burton, D. R.** [Reprint author]; **Moore, J. P.**; **Poignard, P.**
CS **Progenics Pharmaceuticals, Inc., Tarrytown, NY, USA**
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2001) Vol. 41, pp. 240. print.
Meeting Info.: 41st Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, Illinois, USA. September 22-25, 2001.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 7 Nov 2002
Last Updated on STN: 7 Nov 2002
AB Background: CCR5 is a requisite fusion coreceptor for primary HIV-1 isolates and provides a promising target for antiviral therapy. **PRO 140** is an anti-CCR5 monoclonal antibody that inhibits HIV-1 entry at concentrations that do not affect CCR5's chemokine receptor activity, and **PRO 140** mediates genetic subtype-independent inhibition of HIV-1 replication in primary T cells and macrophages (Trkola et al., J. Virol. 75:579, 2001). However, to date no published study has compared the potency and durability of viral suppression mediated by CCR5-targeting agents in vitro and in vivo. Methods: Viral sensitivity to **PRO 140** following prolonged exposure to this agent was evaluated in PBMC culture in vitro and in a therapeutic animal model of HIV-1 infection (Poignard et al.

Immunity 10:431, 1999). The in vitro studies employed the R5 biological clone HIV-1Case C 1/85 and a p24 readout, whereas the in vivo studies employed SCID mice reconstituted with normal human PBMC and later infected with the R5 isolate HIV-1JR-CSF. Animals were treated with single and multiple intraperitoneal injections of **PRO 140** and monitored for plasma viral RNA (Amplicor assay). Results: In both single-dose and multi-dose settings in vivo, **PRO 140** potently and durably reduced viral loads to undetectable levels. In addition, viruses remained sensitive to **PRO 140** following prolonged periods of exposure both in vitro and in vivo. Conclusions: **PRO 140** demonstrated potent and sustained activity against primary viruses both in vitro and in a well-recognized animal model of HIV-1 infection. These findings underscore the therapeutic potential of CCR5-targeting agents in general and **PRO 140** in particular.

- CC General biology - Symposia, transactions and proceedings 00520
 - Cytology - Animal 02506
 - Cytology - Human 02508
 - Biochemistry studies - Proteins, peptides and amino acids 10064
 - Biophysics - Membrane phenomena 10508
 - Pathology - Therapy 12512
 - Blood - Blood and lymph studies 15002
 - Blood - Blood cell studies 15004
 - Pharmacology - General 22002
 - Pharmacology - Clinical pharmacology 22005
 - Virology - Animal host viruses 33506
 - Immunology - General and methods 34502
 - Immunology - Immunopathology, tissue immunology 34508
 - Medical and clinical microbiology - Virology 36006
- IT Major Concepts
 - Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology
- IT Parts, Structures, & Systems of Organisms
 - PBMC: blood and lymphatics, immune system, peripheral blood mononuclear cell
- IT Diseases
 - HIV-1 infection: immune system disease, viral disease, human immunodeficiency virus 1 infection
 - HIV Infections (MeSH)
- IT Chemicals & Biochemicals
 - CCR5; **PRO 140**: anti-CCR5 monoclonal antibody, human immunodeficiency virus-1 entry inhibitor
- IT Miscellaneous Descriptors
 - Meeting Abstract
- ORGN Classifier
 - Hominidae 86215
 - Super Taxa
 - Primates; Mammalia; Vertebrata; Chordata; Animalia
 - Organism Name
 - human
 - Taxa Notes
 - Animals, Chordates, Humans, Mammals, Primates, Vertebrates
- ORGN Classifier
 - Muridae 86375
 - Super Taxa
 - Rodentia; Mammalia; Vertebrata; Chordata; Animalia
 - Organism Name
 - SCID mouse [severe combined immunodeficiency mouse]: animal model
 - Taxa Notes
 - Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
- ORGN Classifier
 - Retroviridae 03305

Super Taxa

DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms

Organism Name

HIV-1 [human immunodeficiency virus 1]: pathogen, replication, suppression

Taxa Notes

DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

L44 ANSWER 13 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2001:2603 BIOSIS
 DN PREV200100002603
 TI Potent, broad-spectrum inhibition of HIV-1 by the CCR5 antibody
PRO 140.
 AU **Olson, W. C.** [Reprint author]; **Ketas, T. J.** [Reprint author];
Nagashima, K. A. [Reprint author]; **Zhao, L.** [Reprint author]; **Maddon,**
P. J. [Reprint author]; **Moore, J. P.**; **Trkola, A.**
 CS **Progenics Pharmaceuticals, Inc., Tarrytown, NY, USA**
 SO Abstracts of the Interscience Conference on Antimicrobial Agents and
 Chemotherapy, (2000) Vol. 40, pp. 283. print.
 Meeting Info.: 40th Interscience Conference on Antimicrobial Agents and
 Chemotherapy. Toronto, Ontario, Canada. September 17-20, 2000.
 Interscience Conference on Antimicrobial Agents and Chemotherapy; American
 Society of Microbiology.
 DT Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 Conference; (Meeting Poster)
 LA English
 ED Entered STN: 21 Dec 2000
 Last Updated on STN: 21 Dec 2000
 CC Immunology - General and methods 34502
 General biology - Symposia, transactions and proceedings 00520
 Cytology - Animal 02506
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Biophysics - Membrane phenomena 10508
 Pathology - Therapy 12512
 Blood - Blood and lymph studies 15002
 Blood - Blood cell studies 15004
 Pharmacology - General 22002
 Virology - Animal host viruses 33506
 Medical and clinical microbiology - Virology 36006
 Chemotherapy - Antiviral agents 38506
 IT Major Concepts
 Immune System (Chemical Coordination and Homeostasis); Infection;
 Pharmacology
 IT Parts, Structures, & Systems of Organisms
 T cell: blood and lymphatics, immune system; macrophage: blood and
 lymphatics, immune system; peripheral blood mononuclear cells: blood
 and lymphatics, immune system
 IT Chemicals & Biochemicals
 CCR5; **PRO 140**: antiviral-drug, anti-CCR5 antibody;
 RANTES [regulation upon activation normal T cell expressed and
 secreted]
 IT Methods & Equipment
 antiviral therapy: therapeutic method
 IT Miscellaneous Descriptors
 Meeting Abstract; Meeting Poster
 ORGN Classifier
 Retroviridae 03305
 Super Taxa
 DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
 Organism Name
 HIV-1 [human immunodeficiency virus 1]: broad spectrum inhibition,
 pathogen, replication

Taxa Notes

DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

=> => d all tot

L48 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2003:563353 BIOSIS
 DN PREV200300565245
 TI The entry of entry inhibitors: A fusion of science and medicine.
 AU Moore, John P.; Doms, Robert W. [Reprint Author]
 CS Department of Pathology and Laboratory Medicine, University of
 Pennsylvania, 34th and Civic Center Boulevard, 806 Abramson, Philadelphia,
 PA, 19104, USA
 jpm2003@pop.med.cornell.edu; doms@mail.med.upenn.edu
 SO Proceedings of the National Academy of Sciences of the United States of
 America, (September 16 2003) Vol. 100, No. 19, pp. 10598-10602. print.
 ISSN: 0027-8424 (ISSN print).
 DT Article
 LA English
 ED Entered STN: 3 Dec 2003
 Last Updated on STN: 3 Dec 2003
 AB For HIV-1 to enter a cell, its envelope protein (Env) must sequentially
 engage CD4 and a **chemokine** coreceptor, triggering conformational
 changes in Env that ultimately lead to fusion between the viral and host
 cell membranes. Each step of the virus entry pathway is a potential
 target for novel antiviral agents termed entry inhibitors. A growing
 number of entry inhibitors are under clinical development, with one having
 already been licensed by the Food and Drug Administration. With the
 emergence of virus strains that are largely resistant to existing reverse
 transcriptase and protease inhibitors, the development of entry inhibitors
 comes at an opportune time. Nonetheless, because all entry inhibitors
 target in some manner the highly variable Env protein of HIV-1, there are
 likely to be challenges in their efficient application that are unique to
 this class of drugs. Env density, receptor expression levels, and
 differences in affinity and receptor presentation are all factors that
 could influence the clinical response to this promising class of new
 antiviral agents.
 CC Biochemistry studies - Proteins, peptides and amino acids 10064
 Biophysics - Membrane phenomena 10508
 Pathology - Therapy 12512
 Pharmacology - General 22002
 Pharmacology - Clinical pharmacology 22005
 Virology - General and methods 33502
 Immunology - Immunopathology, tissue immunology 34508
 Medical and clinical microbiology - Virology 36006
 Chemotherapy - General, methods and metabolism 38502
 Chemotherapy - Antiviral agents 38506
 IT Major Concepts
 Infection; Pharmacology
 IT Diseases
 HIV-1 infection: immune system disease, viral disease, drug therapy,
 human immunodeficiency virus 1 infection
 HIV Infections (MeSH)
 IT Chemicals & Biochemicals
 AMD070: antiinfective-drug, antiviral-drug; AMD3100:
 antiinfective-drug, antiviral-drug; BMS-806: antiinfective-drug,
 antiviral-drug; **CCR5**; CD4; CXCR4; **PRO-140**
 : antiinfective-drug, antiviral-drug; PRO-542: antiinfective-drug,
 antiviral-drug; SCH-C: antiinfective-drug, antiviral-drug; SCH-D:
 antiinfective-drug, antiviral-drug; T20: antiinfective-drug,
 antiviral-drug; TNX-355: antiinfective-drug, antiviral-drug; UK-427857:
 antiinfective-drug, antiviral-drug; envelope protein

IT Miscellaneous Descriptors
 FDA industry; drug development

ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 human (common): host
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
 Retroviridae 03305
 Super Taxa
 DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
 Organism Name
 HIV-1 (miscellaneous) [Human immunodeficiency virus 1 (species)]:
 pathogen
 Taxa Notes
 DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

RN 155148-31-5 (AMD3100)
 339184-91-7 (CXCR4)
 383198-58-1 (PRO-542)

L48 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2002:207314 BIOSIS
 DN PREV200200207314
 TI Identification of amino acid residues critical for LD78beta, a variant of
 human macrophage inflammatory protein-1alpha, binding to CCR5
 and inhibition of R5 human immunodeficiency virus type 1 replication.
 AU Miyakawa, Toshikazu; Obaru, Kenshi; Maeda, Kenji; Harada, Shigeyoshi;
 Mitsuya, Hiroaki [Reprint author]
 CS Dept. of Internal Medicine II, Kumamoto University School of Medicine,
 1-1-1 Honjo, Kumamoto, 860-0811, Japan
 hm21q@nih.gov
 SO Journal of Biological Chemistry, (February 15, 2002) Vol. 277, No. 7, pp.
 4649-4655. print.
 CODEN: JBCHA3. ISSN: 0021-9258.
 DT Article
 LA English
 ED Entered STN: 20 Mar 2002
 Last Updated on STN: 20 Mar 2002

AB In an attempt to determine which amino acid(s) of LD78beta, a variant of
 human macrophage inflammatory protein-1alpha, plays a critical role in the
 interaction with CCR5, we generated six LD78beta variants with
 an amino acid substituted to Ala at the NH2 terminus of LD78beta. There
 was no significant difference in eliciting Ca2+ flux and chemotaxis among
 the variants with the exception of LD78betaT9A showing a substantially
 reduced activity. The comparative order for human immunodeficiency virus
 type 1 (HIV-1) replication inhibition was: LD78betaP8A > LD78betaD6A >
 LD78betaWT, LD78betaL3A > LD78betaT7A, LD78betaP2A > LD78betaT9A. In
 binding inhibition assays of LD78beta variants using 2D7 monoclonal
 antibody and 125I-labeled macrophage inflammatory protein-1alpha, the
 comparative order was: LD78betaP8A, LD78betaD6A > LD78betaWT > LD78betaL3A
 > LD78betaT7A > LD78betaT9A, LD78betaP2A. The order for CCR5
 down-regulation induction was comparable to that for binding inhibition.
 The present data suggest that Pro-2, Asp-6, Pro-8, and
 Thr-9 are critical for LD78beta binding to CCR5 and HIV-1
 replication inhibition, and that LD78beta binding to CCR5,
 regardless of affinity, is sufficient for the initial signal transduction
 of LD78beta, whereas the greater anti-HIV-1 activity requires the greater
 magnitude of binding. The data also suggest that LD78beta variants with
 appropriate amino acid substitution(s) such as LD78betaD6A and LD78betaP8A
 may represent effective chemokine-based anti-HIV-1 therapeutics

while preserving LD78beta-CCR5 interactions.

CC Cytology - Human 02508
 Biochemistry studies - General 10060
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Biochemistry studies - Minerals 10069
 Biophysics - Membrane phenomena 10508
 Pathology - Therapy 12512
 Pharmacology - General 22002
 Pharmacology - Clinical pharmacology 22005
 Virology - Animal host viruses 33506
 Medical and clinical microbiology - Virology 36006
 Chemotherapy - General, methods and metabolism 38502
 Chemotherapy - Antiviral agents 38506

IT Major Concepts
 Biochemistry and Molecular Biophysics; Infection; Methods and Techniques; Pharmacology

IT Chemicals & Biochemicals
 2D7 monoclonal antibody: PharMingen; CCR5; LD78-beta: antiinfective-drug, antiviral-drug, amino acid substituted variants; amino acid residues; calcium (II) ion; iodine-125-labeled-macrophage inflammatory protein-1-alpha [iodine-125-labeled-MIP-1-alpha]: Amersham Biosciences, Inc.; macrophage inflammatory protein-1-alpha [MIP-1-alpha]: Peprotech, Inc.

IT Methods & Equipment
 ARC-370M Gamma System: Aloka Technical Service Co. Ltd., laboratory equipment; Epics XL: Coulter, laboratory equipment; binding inhibition assays: Bioassays/Physiological Analysis, bioassay method

IT Miscellaneous Descriptors
 chemotaxis; viral replication inhibition

ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 CCR5-Molt4 cell line
 human
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
 Retroviridae 03305
 Super Taxa
 DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
 Organism Name
 R5 human immunodeficiency virus type 1 [R5 HIV-1]: pathogen
 Taxa Notes
 DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses

RN 14127-61-8 (calcium (II) ion)

=> => d his

(FILE 'HOME' ENTERED AT 08:38:57 ON 09 MAR 2004)
 SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:39:07 ON 09 MAR 2004

L1 0 S HB12605 OR HB12606 OR HB12607 OR HB12608 OR HB12609 OR HB1261
 L2 0 S HB() (12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610)
 L3 0 S HB()12() (605 OR 606 OR 607 OR 608 OR 609 OR 610)
 L4 0 S ATCC(L)12() (605 OR 606 OR 607 OR 608 OR 609 OR 610)
 L5 0 S ATCC(L) (12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610)
 L6 32 S 12605 OR 12606 OR 12607 OR 12608 OR 12609 OR 12610
 L7 0 S L6 AND (CCR OR CCR5)
 L8 0 S L6 AND ?CHEMOKIN?

L9 0 S L6 AND (MAB OR MONOCLON? OR ANTIBOD?)
 L10 281 S PA8 OR PA9 OR PA10 OR PA11 OR PA12 OR PA14
 L11 629 S PA() (8 OR 9 OR 10 OR 11 OR 12 OR 14)
 L12 896 S L10,L11
 L13 4 S L12 AND (CDR OR CCR OR CCR5)
 L14 4 S L12 AND ?CHEMOKIN?
 L15 4 S L13,L14
 E OLSON W/AU
 L16 19 S E3,E7,E8
 E OLSON WILL/AU
 L17 69 S E5,E10
 E MADDON P/AU
 L18 84 S E3-E8
 E PROGENIC/PA,CS
 L19 52 S E5-E16
 E PROGEN/PA,CS
 L20 3 S E44-E49
 L21 4 S L12 AND L16-L20
 L22 4 S L15,L21
 L23 258 S PRO() (8 OR 80 OR 9 OR 90 OR 10 OR 100 OR 11 OR 110 OR 12 OR 1
 L24 6 S L23 AND (CDR OR CCR OR CCR5)
 L25 6 S L23 AND ?CHEMOKIN?
 L26 6 S L24,L25
 L27 5 S L26 NOT L22
 SEL DN AN 1
 L28 4 S L27 NOT E1-E3
 L29 8 S L22,L28 AND L1-L28
 E WO99-US30345/AP,PRN
 L30 1 S E3,E4
 SEL RN

FILE 'REGISTRY' ENTERED AT 08:51:33 ON 09 MAR 2004

L31 1 S E1

FILE 'HCAPLUS' ENTERED AT 08:51:55 ON 09 MAR 2004

L32 8 S L29,L30

FILE 'HCAPLUS' ENTERED AT 08:52:09 ON 09 MAR 2004

SEL RN 8

FILE 'REGISTRY' ENTERED AT 08:52:55 ON 09 MAR 2004

L33 4 S E2-E5

FILE 'BIOSIS' ENTERED AT 08:53:19 ON 09 MAR 2004

E OLSSON W/AU

E OLSON W/AU

L34 75 S E3,E7,E8

E OLSON WILL/AU

L35 49 S E4,E6

E MADDON P/AU

L36 86 S E3-E6

E PROGEN/CS

L37 50 S E38 OR PROGENICS?/CS

L38 189 S L34-L37

L39 359 S L23

L40 390 S L10 OR L11

L41 0 S L1-L5

L42 28 S L6

L43 9 S L38 AND L39-L42

FILE 'HCAPLUS, BIOSIS' ENTERED AT 08:55:44 ON 09 MAR 2004

L44 13 DUP REM L32 L43 (4 DUPLICATES REMOVED)